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9902935-7 **18 August 1999 (18.08.1999)** **SE**
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- (84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



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(54) Title: **PHARMACEUTICAL COMPOSITIONS**

(57) Abstract: The present invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being an anticholinergic muscarinic antagonist, for use in the treatment of obstructive airways diseases.

PHARMACEUTICAL COMPOSITIONS

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of obstructive airways diseases.

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In accordance with the present invention, there is therefore provided a pharmaceutical composition comprising, in admixture, a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being an
10 anticholinergic muscarinic antagonist.

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically
15 acceptable salt thereof, and a preparation of a second active ingredient (B) being an anticholinergic muscarinic antagonist for sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]-
20 ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, a preparation of a second active ingredient (B) being an anticholinergic muscarinic antagonist, and instructions for the sequential or separate administration of the preparations to a patient in need thereof.

25 The combination of active ingredients according to the invention is advantageous because it is beneficial in the treatment of obstructive airways diseases including chronic obstructive pulmonary disease (COPD); and asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness).

4-Hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one and pharmaceutically acceptable salts thereof are described in WO 93/24473. The active ingredient (A) is most preferably 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one
5 hydrochloride.

Examples of the active ingredient (B) having anticholinergic activity include the muscarinic antagonists:

- (*endo, syn*)-(±)-3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide (ipratropium bromide);
10 (1α, 2β, 4β, 5α, 7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide (tiotropium bromide);
[7(S)-(1α, 2β, 4β, 5α, 7β)]-9-Ethyl-7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide (oxitropium bromide); and
15 [3R-[3R*[S*(R*)]]]-α-(hydroxymethyl)-α-[2-(methylsulfinyl)ethyl]-benzeneacetic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (revatropate).

Methods of assaying for muscarinic receptor activity are described, for example, by N. Watson et al in *Eur. J. Pharmacol.*, 285(2), 135-142 (1995).

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The pharmaceutical composition of the invention may be prepared by mixing the first active ingredient (A) with the second active ingredient (B). Therefore, in another aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a
25 pharmaceutically acceptable salt thereof, with a second active ingredient (B) being an anticholinergic muscarinic antagonist. The pharmaceutical composition of the invention will typically comprise a total amount of first active ingredient (A) and second active ingredient (B) in the range from 0.05 to 99 %w (per cent by weight), more preferably in the

range from 0.10 to 70 %w, and even more preferably in the range from 0.10 to 50 %w, all percentages by weight being based on total composition.

The first and second active ingredients (A) and (B) may alternatively be administered sequentially or separately in any suitable order to treat obstructive airways diseases. By sequential is meant that the first and second active ingredients are administered one immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The active ingredients may, and indeed usually will, be used in admixture with one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients (A) and (B) employed, the mode of administration, the treatment desired and the disorder indicated. If the active ingredients are administered by inhalation, then the total daily dosage of first active ingredient (A) and second active ingredient (B) together is preferably in the range from 5 to 1500 µg, e.g. from 10 to 1450 µg or from 20 to 1400 µg.

The pharmaceutical composition, pharmaceutical product or kit according to the invention may be administered as divided doses from 1 to 4 times a day, and preferably once or twice a day.

The first and second active ingredients (A) and (B) may be administered topically (to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules,

syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

For example metered dose inhaler devices may be used to administer the active
5 ingredient(s), dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents.

Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Especially
10 preferred propellants are HFA-134a and HFA-227, each of which may be used alone or in combination with other propellants and/or surfactants and/or other excipients.

Nebulised aqueous suspensions or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose
15 formulations.

Dry powder inhalers may be used to administer the active ingredient(s), alone or in combination with a pharmaceutically-acceptable carrier, in the latter case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or
20 multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

25 Tablets and gelatin capsules, which may be coated if desired, containing the active ingredient(s) may, for example, also include one or more diluents, carriers, binders, lubricants or stabilising agents.

Injectable solutions of the active ingredient(s) may also contain, for example, one or more preservatives, stabilising agents, viscosity-regulating agents, emulsifying agents or buffering agents.

5 The present invention further provides the use of a pharmaceutical composition, pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an obstructive airways disease.

Also, the present invention provides a method of treating, or reducing the risk of, an
10 obstructive airways disease in a patient suffering from, or at risk of, the disease, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition of the invention.

Still further, the present invention provides a method of treating, or reducing the risk
15 of, an obstructive airways disease which comprises sequentially or separately administering (in any suitable order) to a patient suffering from, or at risk of, the disease
(a) a (therapeutically effective) dose of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof; and
20 (b) a (therapeutically effective) dose of a second active ingredient (B) being an anticholinergic muscarinic antagonist.

CLAIMS

1. A pharmaceutical composition comprising, in admixture, a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active
5 ingredient (B) being an anticholinergic muscarinic antagonist.
2. A composition according to claim 1, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-
10 one hydrochloride is used.
3. A composition according to claim 1 or claim 2, wherein, as second active ingredient (B), ipratropium bromide, tiotropium bromide, oxitropium bromide or revatropate is used.
15
4. A process for the preparation of a pharmaceutical composition as defined in claim 1 which comprises mixing a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, with a second active ingredient (B) being an
20 anticholinergic muscarinic antagonist.
5. Use of a pharmaceutical composition as claimed in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of an obstructive airways disease.
- 25 6. Use according to claim 5 wherein the obstructive airways disease is chronic obstructive pulmonary disease or asthma.
7. A method of treating, or reducing the risk of, an obstructive airways disease in a patient suffering from, or at risk of, the disease, which comprises administering to the

patient a therapeutically effective amount of a pharmaceutical composition as defined in any one of claims 1 to 3.

8. A method according to claim 7, wherein the obstructive airways disease is chronic
5 obstructive pulmonary disease or asthma.

9. A pharmaceutical product comprising, in combination, a preparation of a first active
ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]-
ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt
10 thereof, and a preparation of a second active ingredient (B) being an anticholinergic
muscarinic antagonist for sequential or separate use in therapy.

10. A product according to claim 9, wherein, as first active ingredient (A), 4-hydroxy-7-[2-
[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one
15 hydrochloride is used.

11. A product according to claim 9 or claim 10, wherein, as second active ingredient (B),
ipratropium bromide, tiotropium bromide, oxitropium bromide or revatropate is used.

20 12. Use of a product as claimed in any one of claims 9 to 11 in the manufacture of a
medicament for the treatment of an obstructive airways disease.

13. Use according to claim 12 wherein the obstructive airways disease is chronic
obstructive pulmonary disease or asthma.

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14. A kit comprising a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-
[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a
pharmaceutically acceptable salt thereof, a preparation of a second active ingredient (B)
being an anticholinergic muscarinic antagonist, and instructions for the sequential or
30 separate administration of the preparations to a patient in need thereof.

15. A kit according to claim 14, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride is used.

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16. A kit according to claim 14 or claim 15, wherein, as second active ingredient (B), ipratropium bromide, tiotropium bromide, oxitropium bromide or revatropate is used.

17. A method of treating, or reducing the risk of, an obstructive airways disease which
10 comprises sequentially or separately administering to a patient suffering from, or at risk of, the disease

(a) a dose of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof; and

15 (b) a dose of a second active ingredient (B) being an anticholinergic muscarinic antagonist.

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9902935-7 18 August 1999 (18.08.1999) **SE**
- (71) Applicant (*for all designated States except US*): **ASTRAZENECA UK LIMITED [GB/GB]**; 15 Stanhope Gate, London W1Y 6LN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **INCE, Francis [GB/GB]**; Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **DIXON, John [GB/GB]**; Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **HOLT, Philip, Ronald [GB/GB]**; Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).
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- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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(54) Title: **PHARMACEUTICAL COMPOSITIONS COMPRISING A 7-(2-AMINOETHYL)-BENZOTHAZOLONE AND AN ANTICHOLINERGIC MUSCARINIC ANTAGONIST**

(57) Abstract: The present invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient (A) being 4-hydroxy-7-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3H)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being an anticholinergic muscarinic antagonist, for use in the treatment of obstructive airways diseases.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/46 A61K31/435 A61K31/43

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBASE, CHEM ABS Data, MEDLINE, EPO-Internal, BIOSIS, CANCERLIT, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 24473 A (BROWN ROGER CHARLES ;CHESHIRE DAVID RANULF (GB): FISON PLC (GB);) 9 December 1993 (1993-12-09) cited in the application page 7, line 22 - line 29; example 6 ---	1-17
Y	IKEDA A. ET AL: "Pharmacological treatment in acute exacerbations of chronic obstructive pulmonary disease." DRUGS AND AGING, (1998) 12/2 (129-137). , XP000986468 page 131, column 2, paragraph 3 -page 132, column 1, paragraph 4 --- -/--	1-17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LURIE A. ET AL: "Long-term management of reversible obstructive airways disease in adults." LUNG, (1990) 168/SUPPL. (154-167). , XP000986437 page 157, paragraph 2 ---	1-17
Y	CHAPMAN K R: "An international perspective on anticholinergic therapy." AMERICAN JOURNAL OF MEDICINE, (1996 JAN 29) 100 (1A) 2S-4S. REF: 19 , XP000986461 abstract ---	1-17
Y	BARNES P.J.: "New therapies for chronic obstructive pulmonary disease." THORAX, (1998) 53/2 (137-147). , XP000986442 page 137, column 1, paragraph 5 -page 138, column 1, paragraph 2 -----	1-17

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 00 03118

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1, 2, 4,-10, 12-15, 17

Present claims 1, 2, 4,-10, 12-15 and 17 relate to a compound defined by reference to a desirable characteristic or property, namely an anticholinergic muscarinic antagonist.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 3, 11 or 16, with due regard to the therapeutic applications mentioned in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/GB 00/03118

Patent document cited in search report	Publication date	Patent family members,	Publication date
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